Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy

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Background: Children with allergy to raw egg white might tolerate low amounts of heated egg. Ovomucoid-specific IgE antibodies have been suggested to be predictors of whether children could tolerate heat-treated egg.
Objective: The aim was to evaluate the clinical usefulness and added diagnostic value of measurements of IgE antibodies to egg white, ovalbumin, and ovomucoid in children with egg allergy.
Methods: One hundred eight patients (median age, 34.5 months) with suspected egg allergy underwent double-blind, placebo-controlled food challenges with raw and heated egg. The outcomes of the challenges were related to the serum concentration of specific IgE antibodies and total IgE by using ImmunoCAP.
Results: Reactions to heated egg white were observed in 38 patients (considered allergic to raw and heated egg), 29 patients reacted to only raw egg white, and 41 patients were tolerant. Correlation was observed between the serologic parameters studied. Receiver operating characteristic analysis showed that egg white ImmunoCAP was useful in the diagnosis of allergy to raw egg white. The positive decision point, based on 95% clinical specificity, was 7.4 kU_A/L, and the negative decision point, based on 95% clinical sensitivity, was 0.6 kU_A/L. For reaction to heated egg white, ovomucoid ImmunoCAP was superior. The positive decision point was 10.8 kU_A/L, and the negative decision point was 1.2 kU_A/L.
Conclusions: Quantitative measurements of specific IgE antibodies to both egg white and ovomucoid and the evaluation against the suggested positive and negative decision points for specific IgE will be useful in the diagnosis of egg allergy.
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Key words: *Egg hypersensitivity, specific IgE, egg white, ovalbumin, ovomucoid, food challenge*

Abbreviations used
PPV: Positive predictive value
ROC: Receiver operating characteristic
SPT: Skin prick test

Allergic reactions to food are frequently seen in infants and young children.[1-3] Egg consumption is widespread all over the world, and eggs are frequently used in almost all baked goods. Hen's egg is one of the most common offending foods that cause IgE-mediated allergy in children,[2-4] and egg white–specific IgE concentrations in serum have been shown to correlate with the outcome of oral food challenge tests,[5] which are the gold standard for good clinical practice in patients with food allergy. Reactions to egg can vary from urticaria and atopic dermatitis to severe systemic responses, such as anaphylaxis, in which the highest prevalence can be found in children with moderate-to-severe atopic dermatitis.[6-8]

A large number of egg-hypersensitive patients will outgrow their allergies with increased age and become tolerant to egg ingestion.[9,10] However, sensitization to egg has been shown to be predictive of an increased risk for later development of inhalant allergy and asthma.[11-13]

Egg white contains more than 20 different glycoproteins. Ovomucoid, ovalbumin, conalbumin, and lysozyme have been identified as the major allergens.[14] The highly glycosylated ovomucoid comprises about 10% of the total egg white protein and has been shown to be the dominant allergen.[14,15] Previous studies have suggested that the allergenicity and antigenicity could be explained by the fact that ovomucoid demonstrates a high stability against protease digestion and heat.[14,16]

Reaction to raw or lightly cooked egg but tolerance to more extensively cooked egg-containing foods is a common finding.[17,18] Children in whom results of oral food challenges with cooked egg are positive have a larger skin prick test (SPT) wheal diameter to egg white than children in whom these challenge results are negative.[19] It has been reported that the levels of ovomucoid-specific IgE antibodies could predict whether children can tolerate heat-treated eggs, such as in baked goods.[16] Children with higher concentrations of IgE antibodies directed against ovomucoid and its sequential epitopes are also less likely to outgrow their egg allergy.[14,20] In addition, levels of IgE antibodies against pepsin-digested ovomucoid have been shown to be useful in distinguishing subjects with positive challenge results from subjects with negative challenge results.[21] They can also predict whether children with contact urticaria to hen's egg are likely to manifest systemic symptoms on ingestion.[22]

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There is a need for more differentiated avoidance advice for patients with egg allergy, depending on the reactivity to raw and heat-treated egg. The measurement of IgE antibodies to ovomucoid could be useful to identify children who could tolerate heated hen's egg, thereby eliminating unnecessary provocations. It is important for the physician, as well as the parents, of children with egg allergy to be aware that children who tolerate cooked egg might still react to uncooked egg protein. The present study was designed to further evaluate the clinical usefulness and added diagnostic value of measurements of IgE antibodies to egg white, ovalbumin, and ovomucoid in children with egg allergy.

METHODS

Subjects

One hundred eight patients with suspected egg allergy referred to our clinic for investigation were enrolled in the study. Patients (male/female ratio, 67/41) ranged in age from 14 months to 13 years (median, 34.5 months) and had mostly atopic dermatitis, asthma, and, in a few cases, gastrointestinal symptoms and anaphylaxis. The patients were divided into 3 groups on the basis of their immediate reactions to oral provocation tests. Group A (n = 38) had positive challenge results for heated egg white (the subjects were considered reactive to both heated and raw egg white), group B (n = 29) consisted of subjects who had positive reactions to raw egg white but negative reactions to heated egg white, and group C (n = 41) consisted of subjects who had negative responses to both raw and heated egg white. Further information about the study groups is found in Table I.

Informed consent was obtained from patients, their parents, or both. The study was approved by the Ethics Committee of Fujita Health University School of Medicine.

Preparation of heated egg white

Heated egg white was prepared by heating liquid egg white at 90°C for 60 minutes. After freeze-drying, the preparation was milled into a powder by using a homogenizer. Raw egg white was prepared by directly freeze-drying liquid egg white before homogenization. The freeze-drying process does not change the allergenicity of egg white, as measured by means of SPTs and RAST inhibition (data not shown).

Food challenge

Double-blind, placebo-controlled food challenges with freeze-dried raw and heated egg white were carried out with the methods described previously.[16] Briefly, oral provocations were conducted by administering, in a titrated manner, up to the amounts equivalent to approximately 1 egg of each egg white preparation mixed in 50 mL of a thick liquid vehicle consisting of the juices from an assortment of fruits. Glucose in the same juice was used as a placebo. After administration of the initial dose of 0.1 mL of the heated egg white preparation, the dose was increased sequentially every 30 minutes to 1 mL and 10 mL and then the remainder of the heated egg white until objective symptoms developed or until the entire challenge dose was ingested. Patients who did not react to heated egg white were then challenged with raw egg white in a similar manner. Reactions that were observed within 2 hours of the final administration were deemed to be immediate, and reactions that occurred more than 2 hours after the final administration were considered to be nonimmediate. Patients who had positive responses to challenge with heated egg white were regarded as allergic to both heated and raw egg white.

Specific and total IgE measurement

Sera from all patients were obtained before the food challenge. Levels of specific IgE antibodies to egg white (code f1), ovalbumin (code f232), and ovomucoid (code f233) and total IgE levels were measured by means of ImmunoCAP by using commercially available tests and reagents, according to instructions from the manufacturer (Phadia AB, Uppsala, Sweden).

Statistical analysis

The Mann-Whitney *U* test (2-tailed) was used for pairwise comparisons of continuous parameters (age, total IgE concentrations, and specific IgE concentrations) between study groups. The χ^2 test (2-tailed) was used for pairwise comparison of categorical data (sex, <2 years of age, and symptoms) between study groups. The Spearman rank order correlation coefficient (r_s) was used to measure the strength of the relationship between total IgE and specific IgE antibody levels.

Receiver operating characteristic (ROC) curves[23] were constructed for ImmunoCAP specific IgE and total IgE, with the food challenge result as reference, first by using patients reacting to raw egg white (group A+B) as the diseased group and patients tolerating both heated and raw egg white (group C) as the control group and second by using patients reacting to heated egg white (group A) as the diseased group and patients tolerating heated egg white (group B+C) as the control group.

The diagnostic performance, in terms of sensitivity and specificity, for each test was calculated for the traditional cutoff level of 0.35 kU_A/L, the optimal cutoff level selected from the ROC curve (ie, the cutoff level closest to the upper left corner in the ROC curve optimizing both sensitivity and specificity), the cutoff level producing a specificity of at least 95% (here called the positive decision point), and finally the cutoff level producing a sensitivity of at least 95% (here called the negative decision point). The term *positive decision point* is used because with a specificity of at least 95%, the proportion of false-positive observations in the control group is limited to less than 5%, which favors the positive predictive value (PPV). Correspondingly, the limited proportion of false-negative observations in the disease group for the negative decision point favors the negative predictive value.

RESULTS

Thirty-eight patients (group A) had immediate hypersensitivity reactions to heated egg white when challenged. They were considered allergic to both heated and raw egg white. Of the 70 patients who tolerated heated egg white, 29 reacted to raw egg white at provocation (group B), and 41 were tolerant to both heated and raw egg white (group C). There were no differences in symptoms and the severity of reactions during the challenge tests between groups A and B (data not shown). The patient characteristics are shown in Table I. The patients in groups B and C were very similar regarding their clinical history of symptoms. Almost all had atopic dermatitis, and about 1 in 5 had asthma. The patients who reacted to heated egg white (group A) had similar frequencies of diagnosed atopic dermatitis and asthma but a higher rate of diagnosed allergy to other foods than egg compared with patients tolerant to heated egg. This severe group even contained 3 children who had experienced food-induced anaphylaxis.

The severity of the egg white allergy was associated with higher total serum IgE levels, as well as higher levels of specific IgE antibodies to egg white, ovalbumin, and ovomucoid (Fig 1 and Table II). Two of the children with a history of anaphylaxis had high levels and the third had low levels of specific IgE to egg white (33.3, 48.6, and 1.0 kU_A/L), ovalbumin (33.5, 55.9, and 1.2 kU_A/L), and ovomucoid (25.9, 20.7, and 1.2 kU_A/L).

There was a very strong correlation between the specific IgE antibody levels to ovalbumin and egg white (r_s = 0.97) and a slightly lower correlation between specific IgE to ovomucoid and egg white (r_s = 0.85, data not shown). The correlation between the total IgE levels and the egg white–specific IgE concentrations in the subjects studied was much lower (r_s = 0.46).

Because of the overlap of specific IgE levels between the group of patients reacting to challenge and the tolerant patients, the traditional 0.35 kU_A/L assay cutoff was not useful in these children with suspected egg allergy (Table III). The low clinical

TABLE I. Patient characteristics

	Group A	Group B	Group C
No.	38	29	41
IHR at provocation			
Heated egg white	+	−	−
Raw egg white	ND	+	−
Male/female sex (n)	27/11	17/12	23/18
Age (mo), median (range)	36 (16-137)	30 (14-72)	33 (18-156)
Patients <2 y of age, no. (%)	8 (21%)	10 (34%)	10 (24%)
Diagnosis as reported, no. (%)			
Asthma	10 (26%)	5 (17%)	9 (22%)
Atopic dermatitis	33 (87%)	28 (97%)	41 (100%)
Allergic rhinitis	1 (3%)	0	0
Allergic conjunctivitis	1 (3%)	0	0
Other food allergies	12 (32%)	1 (3%)*	0†
Anaphylaxis	3 (8%)	0	0

IHR, Immediate hypersensitivity reaction; *ND*, not determined.
Significant difference from group A: *$P < .01$, †$P < .001$.

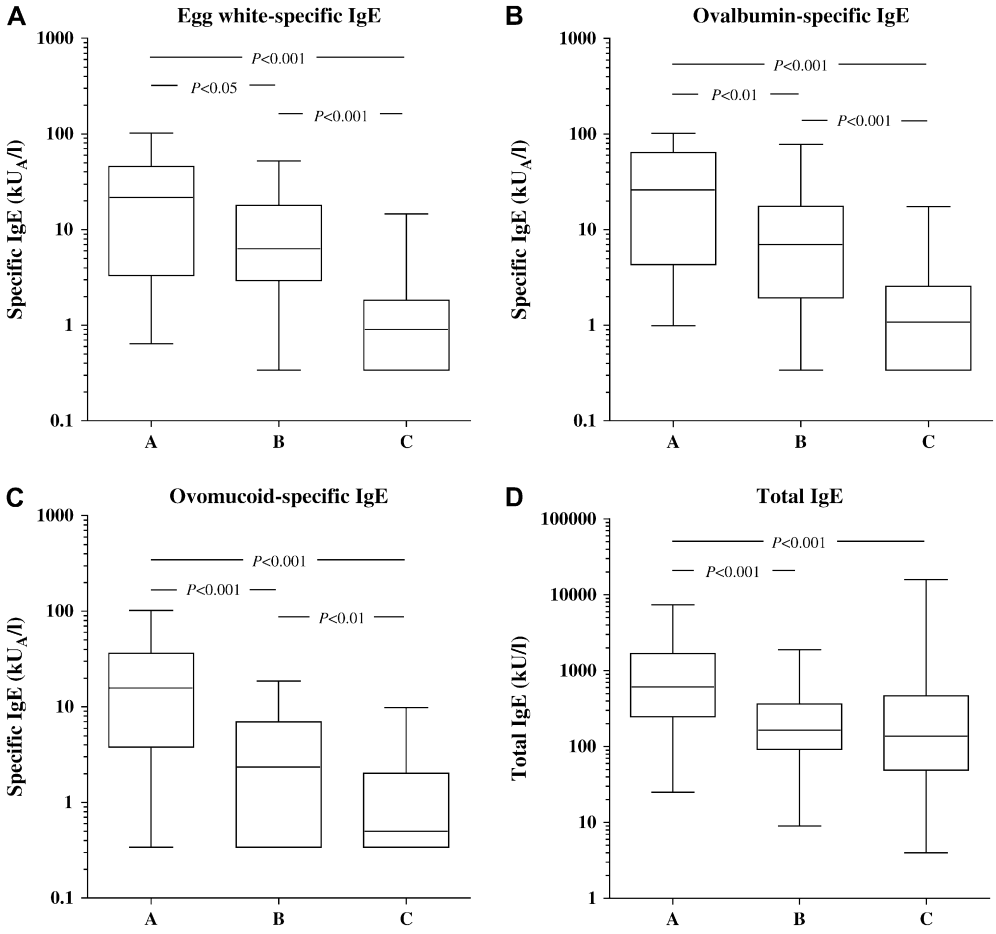

FIG 1. Serum concentrations of specific IgE antibodies to egg white **(A)**, ovalbumin **(B)**, and ovomucoid **(C)** and total IgE **(D)** in children allergic to raw and heated egg white (ie, group A), children allergic to only raw egg white (ie, group B), and children tolerant to both raw and heated egg white (ie, group C).

specificity means that patients cannot be recommended to avoid egg consumption only because of specific serum IgE levels greater than 0.35 kU$_A$/L.

At the optimal cutoff point selected from ROC curves, the specific IgE antibodies to egg white were slightly better compared with the specific IgE antibodies to ovalbumin and ovomucoid in differentiating between patients allergic to raw egg white and tolerant patients (Fig 2, *A*). The total IgE test was not useful. The optimal cutoff point for egg white ImmunoCAP, 2.82 kU$_A$/L, resulted in a clinical sensitivity of 81% and a specificity of 85%.

TABLE II. Serologic analysis

	Group A	Group B	Group C
Total IgE (kU/L), median (range)	605 (25-7350)	165 (9-1900)	137 (4-15840)
Specific IgE (kU_A/L), median (range)			
Egg white	21.6 (0.64->100)	6.3 (<0.35-52.0)	0.90 (<0.35-14.6)
Ovalbumin	26.2 (0.99->100)	7.0 (<0.35-78.3)	1.1 (<0.35-17.4)
Ovomucoid	15.8 (<0.35->100)	2.4 (<0.35-18.6)	0.50 (<0.35-9.8)

Statistically significant differences are shown in Fig 1.

TABLE III. Positive and negative decision points and optimal cutoff points using specific IgE antibody measurements obtained from challenge with raw or heated egg white

	Raw egg white (groups A+B vs group C)			Heated egg white (group A vs groups B+C)		
Challenge food	**Egg white (f1)**	**Ovalbumin (f232)**	**Ovomucoid (f233)**	**Egg white (f1)**	**Ovalbumin (f232)**	**Ovomucoid (f233)**
Assay cutoff point*						
Specific IgE concentration (kU_A/L)	0.36	0.37	0.37	0.36	0.37	0.37
Sensitivity, specificity	97%, 29%	97%, 32%	87%, 41%	100%, 20%	100%, 21%	97%, 36%
PPV, NPV	69%, 86%	70%, 87%	71%, 65%	40%, 100%	41%, 100%	45%, 96%
Optimal cutoff point†						
Specific IgE concentration (kU_A/L)	2.82	3.88	2.26	7.38	6.33	4.40
Sensitivity, specificity	81%, 85%	76%, 83%	73%, 83%	66%, 79%	74%, 73%	76%, 81%
PPV, NPV	90%, 73%	88%, 68%	88%, 65%	62%, 81%	60%, 84%	69%, 86%
Positive decision point						
Specific IgE concentration (kU_A/L)	7.38	9.84	5.21	30.70	29.30	10.80
Sensitivity, specificity	57%, 95%	58%, 95%	52%, 95%	42%, 96%	47%, 96%	55%, 96%
PPV, NPV	95%, 57%	95%, 58%	95%, 55%	84%, 75%	86%, 77%	88%, 80%
Negative decision point						
Specific IgE concentration (kU_A/L)	0.60	0.79	ND	0.85	1.17	1.16
Sensitivity, specificity	96%, 39%	96%, 46%	ND	97%, 36%	97%, 36%	97%, 53%
PPV, NPV	72%, 84%	74%, 86%	ND	45%, 96%	45%, 96%	53%, 97%

NPV, Negative predictive value; *ND*, not determined.
*0.35 kU_A/L.
†Defined as the shortest distance to the ROC.

In the diagnosis of allergy to heated egg white, the test for ovomucoid-specific IgE antibodies was superior (Fig 2, *B*). The optimal cutoff point was 4.40 kU_A/L, which resulted in a sensitivity of 76% and a specificity of 81%. In the diagnosis of allergy to heated egg white, the diagnostic value of specific IgE antibodies to whole egg white and ovalbumin were almost comparable.

Positive decision points based on at least 95% clinical specificity in the diagnosis of allergy to raw egg white were 7.38 kU_A/L for egg white, 9.84 kU_A/L for ovalbumin, and 5.21 kU_A/L for ovomucoid (Table III). The corresponding negative decision points, based on 95% clinical sensitivity for specific IgE antibodies to egg white and ovalbumin, were 0.60 and 0.79 kU_A/L, respectively. The negative decision point for ovomucoid-specific IgE could not be determined because more than 5% of the patients reacting to the raw egg white challenge had specific IgE concentrations of less than the cutoff point (0.35 kU_A/L). The egg white and ovalbumin ImmunoCAP tests showed similar performance in the diagnosis of allergy to raw egg white at the positive decision point. The ovalbumin ImmunoCAP was slightly better at the negative decision point.

For reaction to heated egg white challenge, the positive decision points were 30.70 kU_A/L for egg white, 29.30 kU_A/L for ovalbumin, and 10.80 kU_A/L for ovomucoid. The corresponding negative decision points were 0.85, 1.17, and 1.16 kU_A/L for specific IgE antibodies to egg white, ovalbumin, and ovomucoid, respectively. The ovomucoid ImmunoCAP test showed the best performance in the diagnosis of allergy to heated egg white at both decision points (Table III).

The specific serum IgE antibody concentrations resulting in PPVs not less than 95%, indicating a greater than 95% probability to react to raw egg white at challenge in this particular study population, was greater than 10 kU_A/L for egg white, greater than 12 kU_A/L for ovalbumin, and greater than 6.2 kU_A/L for ovomucoid. The corresponding levels for reactions to the heated egg white challenge were greater than 62 kU_A/L for egg white, greater than 100 kU_A/L for ovalbumin, and greater than 20 kU_A/L for ovomucoid.

DISCUSSION

This study demonstrates that quantitative measurements of specific IgE antibodies, both toward egg white and ovomucoid, are useful in the management of children with egg allergy. Specific IgE antibody levels to egg greater than 7 kU_A/L were highly indicative of allergy toward raw egg, whereas specific IgE antibodies to ovomucoid greater than 11 kU_A/L were indicative for allergy toward heated egg white. These decision points might guide physicians in their decision on whether to perform food challenges.

Egg allergy is one of the most common food allergies in infants and young children. For the great majority, it is not life-threatening, and management involves exclusion of egg from the diet and regular review, with the expectation that the majority of

children outgrow the allergy.[9] Judgment is required as to when dietary elimination of egg is no longer required. This decision might be helped by demonstrating loss of sensitivity by SPTs or specific IgE tests and, in some cases, a supervised food challenge.[17] There is also a need to decide whether a child can be allowed to ingest small amounts of cooked egg through egg-containing foods while continuing to avoid raw egg or larger amounts of whole egg.

We have been able to show in this study that measurement of specific IgE antibodies toward egg white performed well in the diagnosis of reactions to raw egg white. For the identification of patients who react to heated egg white, measurements of specific IgE antibodies toward ovomucoid showed the best results. This knowledge and the use of our decision points can help the physician to plan when to perform a food challenge and when to postpone.

The gold standard for the diagnosis of food allergy is a double-blind, placebo-controlled challenge, although in clinical practice, especially in infants, open or single-blind challenges are quite useful.[17] In this study we performed double-blind, placebo-controlled challenges for both heated and raw egg white. This would be quite time consuming if carried out in clinical practice each time a child is under investigation for suspected egg allergy. We therefore think that specific IgE antibody levels to egg white and ovomucoid should be used.

The clinical decision points are cutoff levels at which food provocations might be excluded because of the high probability of having a true food allergy (positive decision point) or, on the other end of the scale, the high probability of being tolerant (negative decision point). In some studies the level producing at least 95% PPV or, as estimated with logistic regression, the level with a 95% predicted probability of disease has been used as the basis for the positive decision point.[24,25] However, these decision points are dependent on the composition of the study population. If the prevalence of having symptoms is high (ie, when food allergy is common, as in a group of patients referred to a food allergy specialist), the specific IgE concentration representing the 95% PPV is considerably lower than for patients visiting a general practitioner.[26,27] A more reliable value is the specific IgE cutoff level representing the 95% specificity of the test because this value is not dependent on the prevalence of disease.

In the present study we used specific IgE levels representing the 95% specificity of the tests as the positive decision points and levels representing the 95% sensitivity as the negative decision points. The positive decision point for egg allergy (reactivity to raw egg white) was 7.38 kU_A/L for the egg white ImmunoCAP. When using a cutoff level of 7.4 kU_A/L, nearly 6 of 10 children with true egg allergy have positive results (sensitivity, 57%), but only 1 of 20 tolerant children have positive results (specificity, 95%). In practice this means that when having specific IgE antibodies to egg white of greater than approximately 7 kU_A/L, food provocations could be excluded, and egg avoidance might be recommended.

The negative decision point for egg white ImmunoCAP was 0.60 kU_A/L in the diagnosis of egg allergy. Approximately 1 of 20 children with true egg allergy has a specific IgE antibody concentration of less than the cutoff level (sensitivity, 96%). Nearly 4 of 10 children with true egg tolerance have specific IgE antibody concentrations of less than the cutoff level (specificity, 39%).

The ovalbumin ImmunoCAP showed similar diagnostic performance as the egg white ImmunoCAP at the positive decision point and even slightly better performance at the negative decision point. However, because patients might lack IgE antibodies to ovalbumin while they express IgE antibodies to other egg white allergens (ie, ovomucoid, conalbumin, or lysozyme), it is recommended to primarily use a test based on whole egg white in the diagnosis of egg allergy.

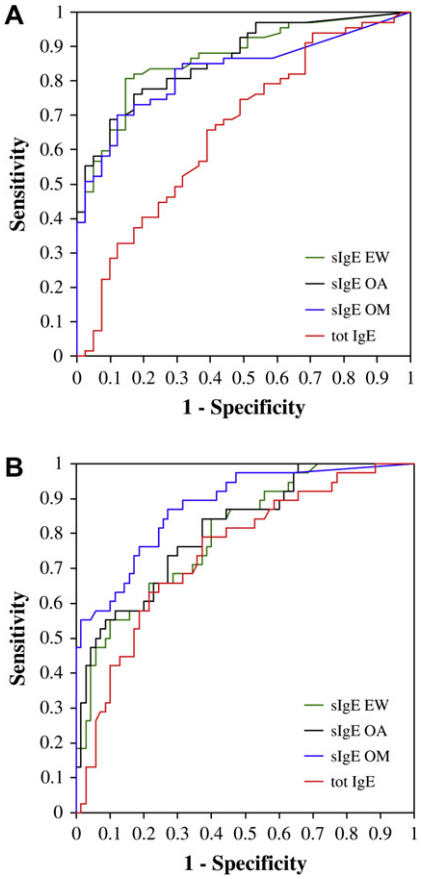

FIG 2. ROC curves showing the performance of the ImmunoCAP tests for specific IgE *(sIgE)* to egg white *(EW)*, ovalbumin *(OA)*, and ovomucoid *(OM)* and total IgE *(tot IgE)* in relation to the diagnosis of children allergic to raw egg white (ie, groups A and B vs group C; **A**) and children allergic to heated egg white (ie, group A vs groups B and C; **B**).

In our study there were 3 children with a history of food-induced anaphylaxis. Two of them had specific IgE levels of greater than the positive decision points for all tests, and the third had low levels that were close to the negative decision points. All 3 reacted to heated egg white when challenged. This indicates that when a case history of severe food-induced allergic reactions is present, specific IgE levels less than or around negative decision points should not be used to recommend food consumption unless food challenges have been performed with negative results.

It has been reported that SPTs with egg white can provide additional information regarding reactions to egg for children with low specific IgE levels (<2.5 kU_A/L).[28] It would have been interesting to know the additional diagnostic information from SPTs in the present study, especially in the children with specific IgE between the negative and positive decision points. However, SPTs were not performed in this study.

The positive decision point for specific IgE antibodies to egg white found in this study is very similar to the decision point at 6 to 7 kU_A/L recommended by Sampson[24] for the diagnosis of allergy to raw egg white. However, he used the specific IgE concentration corresponding to the 95% PPV as the positive decision point. In our study the PPV for egg allergy at the positive decision

point of 7.4 kU_A/L was actually 95%, indicating a similar patient cohort as in the study by Sampson. In a recent article Benhamou et al[25] reported a specificity and PPV of 100% for egg white–specific IgE at 7 kU_A/L in children with suspected egg allergy. It was a retrospective study, and the high specificity and PPV could be explained by the fact that the diagnosis of egg allergy was partially based on case history and specific IgE concentrations.

As far we are aware, no one has previously published positive and negative decision points for the subgroup of children with egg allergy reacting to heated egg white. Our study shows that the measurement of specific IgE antibodies to ovomucoid has a clinical value in distinguishing children who react to heated egg white and children who can eat heated egg. Because heated egg is common in many foods that children are offered, it is of great value for the parents to know what kind of egg product (ie, raw or heated) their children should avoid.

Our data show that children with suspected egg allergy differ in their reactivity to raw and heated egg white. The double-blind, placebo-controlled food challenge is the gold standard in egg allergy, but in cases in which food challenges cannot be performed or when a strong clinical history makes food challenges questionable, specific IgE measurements to egg white and ovomucoid might help the clinician in the decision of recommending avoidance. Specific IgE measurements to ovomucoid are recommended in the diagnosis of allergy to heated egg white. The reason is that ovomucoid mostly retains its allergenicity after extensive heating. It comprises 3 protein domains, each stabilized by 3 intradomain disulfide bonds.[15] The concentration of ovomucoid-specific IgE antibodies at greater than approximately 11 kU_A/L (positive decision point) means a high risk of reacting to heated (as well as raw) egg white, whereas a concentration of less than approximately 1 kU_A/L (negative decision point) means a low risk of reaction to heated egg white, even if the patient might very well react to raw egg white.

The children in our study who passed the heated egg white challenge but failed the challenge with raw egg white were able to tolerate baked egg-containing food, such as cakes and cookies. In our opinion children with specific IgE levels of less than the suggested negative decision point for ovomucoid (<1 kU_A/L) could be given the same recommendation if supported by case history. Other future possibilities are that specific IgE to egg white and ovomucoid could be used for the selection of patients suitable for egg oral immunotherapy.[29]

We conclude that quantitative measurements of specific IgE antibodies by using both egg white and ovomucoid ImmunoCAP will be useful in the diagnosis of egg allergy. Together with the case history and the experience of the physician, the use of positive and negative decision points for specific IgE could decrease the number of necessary food challenges and be helpful in the decision on avoidance recommendations presented to parents of children with suspected egg allergy.

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Clinical implications: Measurement of specific IgE antibodies to egg white and ovomucoid might be helpful in guiding evaluations of children for allergy to raw egg or heated egg (eg, in cakes/cookies).

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